# I. 5-HYDROXY-8-NITROQUINOLINE AND CERTAIN OF ITS DERIVATIVES

# II. REACTION OF ALDEHYDES WITH ORTHOFORMIC ESTERS

BY

ELLIOT NELSON MARVELL

B. S., Brown University, 1943

## AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
IN THE GRADUATE COLLEGE OF THE
UNIVERSITY OF ILLINOIS, 1948

URBANA, ILLINOIS

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# I. 5-HYDROXY-8-NITROQUINOLINE AND CERTAIN OF ITS DERIVATIVES

## Introduction

During the war years a number of antimalarial drugs were prepared at the University of Illinois. One of the intermediates, 5 - hydroxy - 6 - methoxy-8-nitroquinoline, possessed rather unusual properties (1) : it was a brilliant red solid melting at 236-238° d., it was very insoluble in most organic solvents, and it was extremely difficult to alkylate. Since the known nitroquinolinols showed none of these properties, it was proposed to complete the comparison series of *bz*-hydroxy-8-nitroquinolines by the preparation of 5- and 6-hydroxy-8-nitroquinolines.

## Discussion

An unequivocal synthesis of 5-hydroxy-8-nitroquinoline was carried out from *m*-chloroacetanilide. Nitration of this compound was accomplished with fuming nitric acid in a glacial acetic acid-acetic anhydride mixture. The 2-nitro-5-chloroacetanilide was separated from a small amount of its 4-nitro isomer by the method of Lobry de Bruyn (2). The amide was hydrolyzed successfully with sodium ethylate and ethyl alcohol according to the procedure of Verkade and Witjens (3). The desired 5-chloro-8-nitroquinoline was prepared by a Skraup reaction according to the directions of Fourneau, Trefoul, Trefoul and Wancolle (4). Both 5-hydroxy and 5-methoxy-8-nitroquinolines were obtained directly from the chloro compound. The 5-methoxy-8-nitroquinoline was cleaved very readily with dilute hydrochloric acid. The acetate of 5-hydroxy-8-nitroquinoline was hydrolyzed readily by atmospheric moisture.

A sample of 6-hydroxy-8-nitroquinoline was obtained by hydrolytic cleavage of the known 6-methoxy-8-nitroquinoline.

This cleavage was successful when hydrobromic acid in glacial acetic acid was used. The acetate of 6-hydroxy-8-nitroquinoline was completely stable to moisture. Some properties of 7-hydroxy-8-nitroquinoline had been studied previously (5,6). Table I lists the melting points and colors of these nitroquinolinols. The isomeric 5-nitro-6-hydroxyquinoline is included for comparison.

TABLE I

| Compound | M.P. (°C.) | Color |
|---|---|---|
| 5-hydroxy-6-methoxy-8-nitroquinoline | 236-238° d. | red |
| 5-hydroxy-8-nitroquinoline | 261° d. | orange |
| 6-hydroxy-8-nitroquinoline | 242° d. | tan |
| 7-hydroxy-8-nitroquinoline | 255° d. | yellow |
| 5-nitro-6-hydroxyquinoline | 139-140° | yellow |

It is interesting to note that all 8-nitroquinolinols have very high melting points. The chemical properties of 5- and 7-hydroxy-8-nitroquinolines are similar but differ markedly from those of 6-hydroxy-8-nitroquinoline.

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## II. REACTION OF ALDEHYDES WITH ORTHOFORMIC ESTERS

### Introduction

When hydroxypivaldehyde was treated with ethyl orthoformate the product was not the expected diethyl acetal but

was instead 3,3-diethoxy-2,2-dimethylpropyl formate. An examination of the literature showed that this result was novel in type. Accordingly an investigation of the recation of hydroxyaldehydes with orthoformic esters was undertaken.

## Discussion

A number of hydroxyaldehydes have been prepared and allowed to react with ethyl orthoformate in anhydrous ethanol in the presence of dry ammonium chloride. The hydroxyaldehydes as well as the products which were identified are shown in Table II.

TABLE II

| Compound | Products | Overall Yield |
|---|---|---|
| Hydroxypivaldehyde | formic ester[2] | 32% |
| [1]Hydroxypivaldehyde diethyl acetal | no formic ester | ..... |
| Acetaldol | hydroxy acetal 5%[2] formic ester 95% | 24% |
| Propionaldol | hydroxy acetal 50% formic ester 50% | 29% |
| | 2,4-diethyl-5-methyl-6-ethoxy-1,3-dioxane | 20% |
| Isobutyraldol | 2,4-diisopropyl-5,5-dimethyl-6-ethoxy-1,3-dioxane | 80% |
| $\delta$-Hydroxyvaleraldehyde | 2-ethoxytetrahydropyran | 82% |
| Phenylglyoxal | phenylglyoxal diethyl acetal | 83% |

[1]Treated also with ethyl formate and no formic ester produced.
[2]Hydroxy acetal is an abbreviation for the diethyl acetal of the corresponding hydroxyaldehyde. Formic ester is an abbreviation of the formic ester of the hydroxyaldehyde diethyl acetal.

The mixtures of hydroxy acetals and their formic esters could not be separated by fractional distillation with a small packed column. The proportion of products present in the mixtures was estimated from carbon-hydrogen analyses. In each case the products were identified by saponification of the ester and isolation of the metallic formate and the pure hydroxy acetal. Failure to isolate any formic ester from the treatment of hydroxypivaldehyde diethyl acetal with ethyl formate or ethyl orthoformate showed that the production of the formic ester occurred by a process other than ester interchange.

Three $\alpha$-hydroxyaldehydes, glycolaldehyde, lactic aldehyde, and $\alpha$-hydroxyisobutyraldehyde, also were treated with ethyl orthoformate. Although both hydroxy acetals and their formic esters appear to be formed in each case, identification of the products has not been completed. Two additional $\beta$-hydroxyaldehydes, salicylaldehyde and hydracrylic aldehyde, and one $\gamma$-hydroxyaldehyde, $\gamma$-hydroxybutyraldehyde, produced compounds or mixtures which were not identified.

The results show that the products obtained from the reaction of hydroxyaldehydes with orthoformic esters are not readily predictable, and the reaction is not often of synthetic value.

## VITA

The writer was born in New Bedford, Massachusetts, September 10, 1922. He attended the public schools of that city and was graduated from New Bedford High School in June, 1940. In the fall of that year he entered Brown University in Providence, R. I., and received the B. S. degree in Chemistry in October, 1943. That same month he enrolled in the Graduate College of the University of Illinois where he held a teaching assistantship for one semester. From February, 1944, to June, 1945, the author was employed by the University of Illinois as a chemist for the National Defense Research Council. In June, 1945, his graduate work was interrupted by illness. Returning to the University of Illinois in September, 1946, he was an American Chemical Society Predoctoral Fellow and since October, 1947, has held a University Fellowship.

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